REMARKS

Claims 9-12 are pending and under consideration in this application. Claims 9 and 12 have been amended and support for these amendments can be found throughout the specification, e.g., at page 4, lines 1-17. These amendments add no new matter.

Rejections Under 35 U.S.C. § 112, first paragraph (Enablement)

Claims 9-12 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

According to the Office Action, the claims "broadly embrace[s] fragments of the heavy chain and light chain variable regions that do not include all six CDRs and do not bind CCR2 and are nonenabling...."

Applicants respectfully disagree with this characterization for the reasons of record (see Reply to Office Action dated May 15, 2006). However, solely in the interest of expediting prosecution of this application, independent claims 9 and 12 have herein been amended to recite that "the heavy chain comprises the amino acid sequence of SEQ ID NO:17" and "the light chain comprises the amino acid sequence of SEQ ID NO:12.

Applicants respectfully submit that the aforementioned amendments render this rejection moot.

Rejections Under 35 U.S.C. § 102 (Anticipation)

(1) Claims 9-12 are rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Horvath et al. [a](PCT Publication No. WO 01/70266 A2).

According to the Office Action,

> Horvath et al. [a] teach a humanized CCR2 specific antibody and antigen-binding fragments thereof comprising a heavy chain sequence comprising the variable heavy domain of SEQ ID NO:17 and the modified human IgG1 constant region comprising two mutations...which is identical to SEQ ID NO:110 and a light chain sequence comprising the variable light

domain of SEQ ID NO:12 and the human kappa constant region and the immunoglobulin comprises two heavy chains and two light chains[.]

.....

Thus, Horvath et al. [a] anticipate the claims.

Applicants respectfully traverse this rejection and submit the following remarks to show that the claimed invention is not anticipated by Horvath et al. [a].

In order to establish a *prima facie* case of inherent anticipation, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." (MPEP § 2112, citing *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)) (emphasis in original). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." (underlining added) (MPEP § 2112, citing *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)). "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic"(underlining added) (MPEP §2112, citing *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993)).

Independent claim 9 is drawn to a humanized immunoglobulin or antigen binding portion thereof having binding specificity for CCR2 and having a heavy chain and a light chain, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO:17 and the amino acid sequence of SEQ ID NO:110 or a portion thereof, and the light chain comprises the amino acid sequence of SEQ ID NO:12. Independent claim 12 is drawn to a humanized immunoglobulin or antigen binding portion thereof having binding specificity for CCR2 and having a heavy chain and a light chain, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO:17 and the amino acid sequence of SEQ ID NO:110 or a portion thereof, and the light chain comprises the amino acid sequence of SEQ ID NO:12 and the amino acid sequence of SEQ ID NO.:112 or a portion thereof. Thus, the claims recite that the humanized immunoglobulin have a specific amino acid sequence for the heavy chain constant region.

As provided in the Declaration Under 37 CFR 1.132 of Theresa O'Keefe, Ph.D. (hereafter referred to as "the Declaration"), Horvath et al. [a] do not provide an actual amino acid sequence for any human IgG1 constant region much less the specific amino acid sequence listed in the claims. Instead, Horvath et al. [a] disclose that humanized antibodies

> can comprise a constant region from ... the γ (e.g., γ 1, γ 2, γ 3, γ 4), μ, α (e.g., α 1, α 2), δ or ε heavy chains of human antibodies, including allelic variants. A particular constant region (e.g., IgG1), variant or portions thereof can be selected in order to tailor effector function. For example, an mutated constant region (variant) can be incorporated into a fusion protein to minimize binding to Fc receptors and/or ability to fix complement...(underlining added) (Horvath et al. [a] page 17, lines 16-22).

This does not disclose specific sequences or haplotypes but rather classes or genera. The only other discussion of constant regions in Horvath et al. [a] is specific to anti-CD18 antibodies, not anti-CCR2 antibodies, and again does not refer to a specific IgG1 amino acid sequence. The cited paragraph can be found, e.g., at page 25 of the Horvath PCT Publication which states

> Preferred anti-CD18 antibodies for administration to humans include humanized YFC51.1 antibodies ... such as LDP-01 (humanized YFC51.1 which comprises a human γ1 heavy chain constant region having two mutations ($Leu^{235} \rightarrow Ala^{235}$ and $Gly^{237} \rightarrow Ala^{237}$) which reduce binding to Fcγ receptors. (underlining added).

Therefore, Horvath et al. disclose that for a given anti-CCR2 antibody, if a constant heavy chain is included, there are numerous classes or types of heavy chain constant regions that can be present, namely the γ (e.g., γ 1, γ 2, γ 3, γ 4), μ, α (e.g., α 1, α 2), δ or ε heavy chains). Further, as provided in the Declaration, the Office Action incorrectly characterize the term "human IgG1 constant region" as referring to only one amino acid sequence. In fact, there are different allotypes of human IgG1 constant regions in nature. Therefore, this term does not necessarily suggest a particular amino acid sequence but instead refers to a class having many different human IgG1 allotypes. Nothing the Horvath [a] reference suggests human IgG1 sequence over other isotypes or the particular human IgG1 sequence over other human IgG1 allotypes. Therefore, the generic human IgG1 constant region disclosure in the Horvath [a]

reference is not identical to the specific amino acid sequence provided in SEQ ID NO:110 of the claims. Thus, Applicants respectfully submit that given the numerous possibilities of potential human antibody constant region sequences provided above, the CCR2-specific antibodies disclosed in Horvath et al. [a] would not necessarily have a heavy constant chain amino acid sequence of SEQ ID NO:110 which is required by the instant claims. At best, the reference discloses classes and not species. In addition, the specific mutations at residues 235 and 237 are only disclosed with regard to anti-CD18 antibodies. Therefore, Horvath et al. [a] does not anticipate the instant claims.

In view of the above remarks, Applicants respectfully request that the Examiner withdraw the rejection.

(2) Claims 9-12 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Horvath et al. [b] (U.S. Patent No. 6,663,863).

According to the Office Action,

> Horvath et al. [b] teach a humanized CCR2 specific antibody and antigen-binding fragments thereof comprising a heavy chain sequence comprising the variable heavy domain of SEQ ID NO:17 and the modified human IgG1 constant region comprising two mutations…which is identical to SEQ ID NO:110 and a light chain sequence comprising the variable light domain of SEQ ID NO:12 and the human kappa constant region and the immunoglobulin comprises two heavy chains and two light chains[.]
>
> ….
>
> Thus, Horvath et al. [b] anticipate the claims.

Applicants respectfully traverse this rejection and submit the following remarks to show that the claimed invention is not anticipated by Horvath et al. [b].

The standard for inherent anticipation is set forth above as are descriptions of the claims.

The disclosure regarding heavy chain constant regions is the same in Horvath et al. [b] as in Horvath et al. [a] discussed above. Thus, given the numerous potential human constant region amino acid sequences provided by Horvath et al. [b], a CCR2-specific antibody would not necessarily have a heavy chain amino acid sequence of SEQ ID NO:110 as is required by the instant claims. Therefore, Horvath et al. [b] does not anticipate the instant claims.

In view of the foregoing, Applicants respectfully request that the Examiner withdraw the rejection.

Rejections Under 35 U.S.C. § 103(a) (Obviousness)

(1) Claims 9-12 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over LaRosa et al. [a] (U.S. Patent No. 6,727,349 B1) or LaRosa et al. [b] (U.S. Patent No. 6,696,550) in view of Bonnefoy et al. (PCT Publication No. WO 99/58679).

Applicants respectfully request that the Examiner remove these rejections because the present application was subject to an obligation to assign to Millennium Pharmaceuticals, Inc. at the time the invention was made and was recorded with the USPTO on April 4, 2004 (at reel/frame 014518/0285), and both U.S. Patent Nos. 6,727,349 and 6,696,550 were assigned to Millennium Pharmaceuticals Inc. (reel/frame 011196/0894 and 012511/0380, respectively) at the time the invention was made.

(2) Claims 9-12 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Hancock et al. (U.S. Patent Publication No. 2002/0042370 A1) in view of Bonnefoy et al. (referenced above).

According to the Office Action,

> Hancock et al teach a humanized CCR2 specific antibody and antigen-binding fragments thereof comprising the heavy chain variable domain of SEQ ID NO:17 and a light chain variable domain of SEQ ID NO:12....Hancock et al does not specifically teach a humanized CCR2 specific antibody or antigen-binding fragment thereof comprising the modified human IgG1 heavy chain constant region of SEQ ID NO:110. This deficiency is made up for by the teachings of Bonnefoy et al. (see Office Action at page 8, line 20, to page 9, line 5).

Applicants respectfully traverse this rejection and provide the following remarks to show that the claimed humanized antibodies would not have been obvious in view of the cited references.

As discussed above, the claims recite a humanized CCR2 specific immunoglobulin or antigen binding portion thereof having, amongst other things, a specific heavy chain amino acid sequence.

Hancock et al. disclose antibodies having the heavy and light variable regions of a humanized 1D9 monoclonal antibody, e.g., SEQ ID NO: 17 and SEQ ID NO:12, respectively. However, as acknowledged by the Office Action, "Hancock et al does not specifically teach a humanized CCR2 specific antibody or antigen-binding fragment thereof comprising the modified human IgG1 heavy chain constant region of SEQ ID NO:110" (underlining added) as required by the instant claims (see page 9, lines 2-5 of the Office Action). In fact, there is no discussion in the Hancock et al. reference of a preference for any particular isotype for the heavy chain constant region. For example, there is no teaching or suggestion for using a heavy chain constant region of IgG1 over, for example, an IgG2, IgG3, IgG4, IgM, etc. In addition, there is no teaching or suggestion of using a heavy chain constant region from a particular IgG1 allotype over all other human IgG1 allotypes known at the time of filing. Moreover, nothing in the Hancock reference suggests a preference for the particular mutations made to the IgG1 sequence covered by SEQ ID NO:110. Hancock only says to include a constant region. There is no suggestion at all that the CCR2 specificity should be combined with the ability or inability to fix complement.

Bonnefoy et al. is alleged to cure the aforementioned deficiency of Hancock et al. Bonnefoy et al. disclose a completely different humanized antibody (a humanized CD23 (FcεRII)-specific antibody) that binds to a completely different target than the claimed antibodies. An exemplary humanized CD23-specific antibody disclosed by Bonnefoy contains a portion of SEQ ID NO:110.

Applicants respectfully submit that even if the skilled artisan would have read Bonnefoy et al., there was no suggestion or motivation to select a specific IgG1 heavy chain constant region amino acid sequence of SEQ ID NO:110 (nor a light chain constant region amino acid sequence of SEQ ID NO:112) to make the instantly claimed humanized CCR2-specific antibodies. Bonnefoy et al. disclose that a constant region for a humanized anti-CD23 antibody

can be selected according to the functionality required. "The antibody may be an IgG, such as IgG1, IgG2, IgG3 or IgG4; or IgM, or IgA, IgE, or IgD or a modified variant thereof. The constant domain of the antibody heavy chain may be selected accordingly. The light chain constant domain may be a kappa or lambda domain." (Bonnefoy et al., page 7, lines 1-6). Bonnefoy et al. also states that the constant regions can be modified, e.g., at positions 235 and 237 (page 7, lines 13-14). There is no teaching to pair the two elements of the claimed antibody, namely CCR2 specificity and decrease complement fixation.

As provided in the Declaration, a disclosure of a heavy chain constant region for one antibody does not suggest that the particular constant region should be selected for the heavy chain constant region of a completely different antibody to a completely different target. In fact, several other references were available at the time of filing that disclose other humanized antibodies and suggest a preference for a completely different heavy chain constant sequence. For example, U.S. Patent No.: 6,682,736 describes humanized anti-CTLA antibodies and discloses a preference of sequences for the heavy chain constant region from an IgG2 or IgG4. Furthermore, even if a skilled artisan were to chose an IgG1 heavy chain constant region from all other available isotypes, the Declaration provides that there are at least five different allotypes of IgG1, and several different known mutations of these sequences. There was clearly no suggestion that SEQ ID NO:110 (or SEQ ID NO:112), *per se*, should be selected for humanization of the CCR2-specific antibodies of Hancock et al. in lieu of any of the other aforementioned sequence possibilities disclosed for a humanized heavy chain constant region. There is no suggestion to combine anti-CCR2 functionality with any particular constant region and no suggestion to combine anti-CCR2 functionality with the mutation at residues 235 and 237 to decrease complement fixation.

Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

(3) Claims 9-12 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over LaRosa et al. [c] (WO 01/57226 A1) in view of Bonnefoy et al. (referenced above).

According to the Office Action,

> LaRosa et al. [c] teach a humanized CCR2 specific antibody and antigen-binding fragments thereof comprising the heavy chain variable domain of SEQ ID NO:17 and a light chain variable region of SEQ ID NO:12.... Hancock et al does not specifically teach a humanized CCR2 specific antibody or antigen-binding fragment thereof comprising the modified human IgG1 heavy chain constant region of SEQ ID NO:110. This deficiency is made up for by the teachings of Bonnefoy et al. (see Office Action at page 11, lines 9-20).

Applicants respectfully traverse this rejection. LaRosa et al., like Hancock et al., disclose antibodies having the heavy and light variable regions of a humanized 1D9 monoclonal antibody, e.g., SEQ ID NO: 17 and SEQ ID NO:12, respectively. However, as acknowledged by the Office Action, "LaRosa et al does not specifically teach a humanized CCR2 specific antibody or antigen-binding fragment thereof comprising the modified human IgG1 heavy chain constant region of SEQ ID NO:110" (underlining added) as required by the instant claims (see page 9, lines 2-5 of the Office Action). Instead, LaRosa et al. disclose that the

> human constant region or portion thereof, if present, can be derived from ... the γ (e.g., γ 1, γ 2, γ 3, γ 4), μ, α (e.g., α 1, α 2), δ or ε heavy chains of human antibodies, including allelic variants. A particular constant region (e.g., IgG1), variant or portions thereof can be selected in order to tailor effector function. For example, an mutated constant region (variant) can be incorporated into a fusion protein to minimize binding to Fc receptors and/or ability to fix complement. (LaRosa et al., page 30, line 30 through page 31, line 6).

Thus, LaRosa et al. do not teach or suggest a preference for an IgG1 constant region. Moreover, there is no teaching or suggestion of using a heavy chain constant region from a particular IgG1 allotype. There is also no teaching or suggestion of a preference for the particular mutations made to the IgG1 sequence covered by SEQ ID NO:110.

As discussed supra, there is no teaching or suggestion in Bonnefoy et al. that the particular SEQ ID:110 or SEQ ID NO:112 should be selected over any other human constant region for completely different type of antibody, a humanized CCR2-specific antibody. As provided in the Declaration and discussed above, at the time of filing, many other sequences for heavy chain constant regions were known and used. These include γ (e.g., γ 1, γ 2, γ 3, γ 4), μ, α (e.g., α 1, α 2), δ or ε heavy chain sequences, mutations of these sequences and various

allotypes. Nothing in the LaRosa et al. reference nor the Bonnefoy et al. reference teach or suggest that the particular heavy chain sequence of SEQ ID NO:110 be selected for a humanized anti-CCR2 antibody.

Therefore, in view of the preceding remarks, Applicants respectfully request that the Examiner withdraw the rejection.

CONCLUSION

For the reasons set forth above, applicants submit that all grounds for objection and rejection have been overcome and that all claims are now in condition for allowance, which action is requested.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at the number given below.

The fees for the Petition for a three-month Extension of Time are being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No: 10448-213001.

Respectfully submitted,

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